DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Acknowledgment and entry of the Amendment submitted on 3/7/11 is made. Claims 8-11 and 14-16 are currently pending.

Claim Rejections - 35 USC § 112-Written Description

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 8-11 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In 1999, the United States Patent and Trademark Office ("USPTO") published training materials regarding the examination of patent applications under the written description requirement of 35 U.S.C. § 112, first paragraph. (See http ://www.uspto. gov/web/offices/pac/writtende sc.pdf). Since that time, the case law and technology have developed in such a way as to necessitate a revision of the 1999 training materials. Consequently, this 2008 revision was created to supersede and replace the 1999 training materials. To the extent that any conflict exists between the 1999 training materials and the present materials, the present materials

control. The claims have been evaluated with regard to written description based on the Written Description Guidelines and Training Materials published in 2008/

The instant claims are drawn to "composition capable of eliciting both a cytotoxic T-cell and an antibody based an immune response comprising an immunogenic determinant, wherein the immunogenic determinant comprises a mixture of complexes between a stress induced stress protein and an antigenic peptide fragment, wherein:

the complexes are obtained from a cell which has been infected with a bacterial, protozoal or parasitic intracellular pathogen, which infected cell has been subjected to stress from heat or tumor necrosis factor sufficient to stimulate the presence of stress proteins within the infected cell,

the stress proteins of the stress protein complexes are derived from the infected cell o~ and from the intracellular pathogen,

the antigenic peptide fragment of the stress protein complexes is derived from the intracellular pathogen, and

the immunogenic determinant comprises stress protein complexes which are not purified to homogeneity. "

To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. Applicants have not described the genus of claimed complexes such that the specification might reasonably convey to the skilled artisan that Applicants had possession of the claimed invention at the time the application was filed.

To adequately describe the genus of immunogenic compositions, Applicant must adequately describe the antigenic determinants (immunoepitopes) that elicit a given

directed immune response. However, the specification does not disclose distinguishing and identifying features of a representative number of members of the genus of immunogenic compositions to which the claims are drawn, such as a correlation between the structure of the immunoepitope its recited function (to elicit an directed immune response against a given pathogen(s)), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of vaccines.

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "'Written Description" Requirement (66 FR 1099-1111, January 5,2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by

disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104).

Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed. The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus'" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan et al (Nature Biotechnology 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2).

According to Greenspan et al, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Chothia et al (THE EMBO JOURNAL, 1986, 5/4:823-26) also teach that there is a limit to how much substitution can be tolerated before the original tertiary structure is lost. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of complexes, the skilled artisan could not immediately recognize that Applicants were in possession of the claimed genus of peptides at the time of filing.

The scope of the claim includes numerous structural variants and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification does not describe any members of the claimed genus by complete structure. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus, and thus, that the applicant was not in possession of the claimed genus. The claimed subject matter is not supported by an adequate written description because a representative number of species has not been described.

There are no drawings or structural formulas disclosed of *any* of these immunogenic complexes. There is no teaching in the specification regarding which part of the structure can be varied and still produce a

fragment which can elicit both a cytotoxic T-cell and an antibody based response. Based on the lack of knowledge and predictability in the art, those of ordinary skill in the art would not conclude that the applicant was in possession of the claimed *genus* of complexes.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect specific fragments or complexes which induce both a cytotoxic and antibody based immune response; no specific structures are described. Additionally, none of the examples provided describe or show the use of stress proteins produced by an intracellular-pathogen, nor is there any written description for such stress proteins, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). With regard to (4) the nature of the invention and (5) the state of the prior art, these have been discussed above. One of skill in the art would require guidance, in order to make or use the compositions as instantly claimed.

Response to Applicants' arguments:

Applicants' argue that the Examples on pages 12-18 exemplify the invention for mammalian cells infected with M.bovis, mammalian cells infected with P.Berghei and mammalian cells infected with M.tuberculosis. They argue that the present invention is a crude composition not purified to homogeneity and therefore a specific composition is not required. This has been fully and carefully considered but is not deemed persuasive. The fact that the composition itself may vary, makes it even more pressing that either the specific process (including organisms) be used to replicate the product which is claimed, or the actual product be deposited. **It is unclear what final product is being claimed for patent coverage if the components in the claimed composition are constantly variable.** Additionally, there is no teaching in the specification regarding which part of the structure can be varied and still produce an antigenic fragment which can elicit both a cytotoxic T-cell and an antibody based response. The specific examples pointed to by Applicant are not a 'representative number of species' for the incredibly broad Genus which is claimed. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute adequate written description and an enabling disclosure. While every aspect of a

generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 8-11 and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Srivastava et al (WO 95/24923).

Srivastava et al disclose vaccines and compositions comprising stress protein-peptide complexes. They specifically teach heat shock proteins (HSP) may be used as the stress protein. Srivastava et al define 'stress protein' as a protein whose intracellular concentration increases when exposed to stressful stimuli, is capable of binding to other proteins or peptides, and is capable of releasing the bound proteins in the presence of ATP or low pH. See page 10, lines 9-13. Srivastava et al define stressful stimuli to "include, but [are] not limited to, heat shock, nutrient deprivation, metabolic disruption, oxygen radicals, and infection with intracellular pathogens". See page 10, lines 13-15. Srivastava et al teach that they have discovered that a stress protein-peptide complex

when isolated from a eukaryotic cell infected with a preselected intracellular pathogen and then administered to a mammal can stimulate a cytotoxic T cell response directed against cells infected with the same pathogen. See page 19, lines 1-9. Srivastava et al teach that the stress proteins can accumulate to very high levels in stressed cells, but they occur low to moderate levels in cells that have not been stressed. They give the example of Hsp70 which is hardly detectable at normal temperatures but becomes one of the most actively synthesized proteins in the cell upon heat shock and Hsp90 and Hsp60 are abundant at normal temperatures in almost all mammalian cells, but are even further induced at by heat. See bottom of page 23. Srivastava et al teach that their immunogenic stress protein-peptide complexes may include any complex containing a stress protein and a peptide that is capable of inducing an immune response in a mammal. See page 23, lines 20-27. **The complexes can be prepared from cells infected with an intracellular pathogen as well as cells that have been transformed by an intracellular pathogen**. See page 24, lines 5-10. Pages 46-48 teach that adjuvants and/or pharmaceutically carriers may be used. Page 13, lines 1-15 teach that the complexes may be infected with bacterial, protozoal or parasitic intracellular organisms. Claim 15 specifically recites the 'stress' to be subjection to tumor necrosis factor. However, this is a product-by-process claim (as are all of the claims), "The patentability of a product does not depend upon its method of production. If the product in [a] product-by-process claim is the same as or obvious from a product of the prior art, [then] the claim is unpatentable even though the prior [art] product was made by a different process." In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985)

(citations omitted). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 218 USPQ 289, 292 (Fed. Cir. 1983). There does not appear to be a structural difference between the product claimed and the product taught by the prior art, e.g., the claimed compositions solely comprise an immunogenic determinant any complex comprising a stress protein and an antigenic peptide fragment. Srivastava et al teach that their immunogenic stress protein-peptide complexes may include any complex containing a stress protein and a peptide that is capable of inducing an immune response in a mammal. See page 23, lines 20-27. Srivastava et al specifically teach the complexes can be prepared from cells infected with an intracellular pathogen as well as cells that have been transformed by an intracellular pathogen. See page 24, lines 5-10.

Response to applicant's arguments:

Applicants argue that Strivastava relate only to a single class of mammalian stress protein while the instant claims contain different types of mammalian stress protein and stress proteins from invading pathogen. This argument has been carefully considered but is not commensurate in scope with the claimed invention. There is no mention of different types of mammalian stress proteins in the instant claims. Further, 23. Srivastava et al teach that their immunogenic stress protein-peptide complexes may include any complex containing a stress protein and a peptide that is capable of

inducing an immune response in a mammal. See page 23, lines 20-27. The complexes can be prepared from cells infected with an intracellular pathogen as well as cells that have been transformed by an intracellular pathogen. See page 24, lines 5-10. Pages 46-48 teach that adjuvants and/or pharmaceutically carriers may be used. Page 13, lines 1-15 teach that the complexes may be infected with bacterial, protozoal or parasitic intracellular organisms.

5. Claims 8-11 and 14-16 remain rejected under 35 U.S.C. 102(e) as being anticipated by Srivastava et al (US 5,961,979).

Srivastava teaches a vaccine composition comprising an immunogenic determinant comprising one or complexes between a shock protein and an antigenic peptide from the heat stressing of a cell infected with a bacterial, protozoal or parasitic intra-cellular pathogen (see title, abstract and claims). Srivastava teaches that a vaccine containing a stress protein peptide complex when isolated from cells infected with an intracellular pathogen and then administered to a mammal can effectively stimulate immune response against the pathogen (see column 4, line 60-68 summary of the invention). Srivastava teaches bacteria and protozoa (see column 7, lines 1-15). Srivastava teaches pharmaceutical carriers including aqueous composition and adjuvants (see column 23, lines 19-68). Srivastava teaches a method of producing the stress proteins including heat shock proteins and complex vaccine (see columns 5, 13 and 14). The prior art teaches the claimed invention. . Claim 15 specifically recites the 'stress' to be subjection to tumor necrosis factor. However, this is a product-by-process claim (as are all of the claims), "The patentability of a product does not depend upon its

method of production. If the product in [a] product-by-process claim is the same as or obvious from a product of the prior art, [then] the claim is unpatentable even though the prior [art] product was made by a different process." In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 218 USPQ 289, 292 (Fed. Cir. 1983). There does not appear to be a structural difference between the product claimed and the product taught by the prior art, e.g., the claimed compositions solely comprise an immunogenic determinant any complex comprising a stress protein and an antigenic peptide fragment.

Response to applicant's arguments:

Applicants arguments settle on the fact that there would be no motivation to Srivastava to produce both a cell mediated and a humoral response. This argument has been fully and carefully considered but is not deemed persuasive. The structure claimed is the same as that taught by Srivastava so it would possess the same inherent function.

Strivastava does teach that for immunizing against an intracellular pathogen it is a necessity to elicit a strong cytotoxic T-cell response. They teach that subunit vaccines were known to produce good humoral immune responses but failed to elicit strong T-cell immune response. Strivastava sought to find a composition which could effectively elicit a T-cell immune response. The HSPs in the complexes were well known in the prior

art, as also taught by, Strivastava for elicity an antibody based immune response. The fact that Strivastava teaches that a strong T-cell immune response was raised does not negate or teach away from there also being an antibody immune response present. Since Strivastava teaches structurally analogous structures, they would inherently produce the same types of immune responses.

Additionally, the instant claims recite 'an immunogenic determinant comprising any induced stress protein and any antigenic peptide *obtained* from, a cell which has been infected with....". Srivastava et al teach an immunogenic determinant comprising any induced stress protein and any antigenic peptide. The claims are product-by-process claims. "The patentability of a product does not depend upon its method of production. If the product in [a] product-by-process claim is the same as or obvious from a product of the prior art, [then] the claim is unpatentable even though the prior [art] product was made by a different process." In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 218 USPQ 289, 292 (Fed. Cir. 1983). There does not appear to be a structural difference between the product claimed and the product taught by the prior art, e.g., the claimed compositions solely comprise an immunogenic determinant any complex comprising a stress protein and an antigenic peptide fragment. While a specific stressor may cause more stress protein and stress protein

complexes to be induced, it does not appear to change the structure of the complex, nor does the claim require a specific level of complex. Srivastava et al do not solely teach constitutively expressed complexes. Srivastava discloses the claimed compositions produced by a stress process and isolated from natural sources, produced in situ. The bacterial heat shock protein (see Table 1 and definitions) is complexed together with an antigenic peptide fragment from a bacteria (see col. 7, line 7 "Chlamydia"), fungus, or protozoa, wherein the heat shock protein complex is isolated from natural sources (see col. 21, line 28). Accordingly, Srivastava et al anticipates the claimed compositions.

Applicants argue that Strivastava describe stress peptide complexes purified to homogeneity. They argue that, accordingly, these complexes can comprise only a single stress protein species. They quote page 28, line 20, of WO 95/24923 "the Hsp-70-peptide complex can be purified to apparent homogeneity using this method". These arguments are not commensurate in scope with the claimed invention. The claims do not require the use of more than one stress peptide. In fact the claims recite the complex is between a stress induced protein [not plural] and an antigenic determinant. Strivastava state that the complex "can" be purified to homogeneity but do not require it. Applicants also argue that their complexes are capable of eliciting both cell-mediated CTL responses as well as humoral antibody response as evidenced by the passage at page 14, lines 8-17, of the specification for support. This passage recites:

In order to determine the immunogenicity of the SP complexes, T cell proliferation assays may be used. Suitable assays include the mixed-lymphocyte reaction (MLR), assayed by tritiated thymidine uptake, and cytotoxicity assays to determine the release of 51Cr from target cells, see 'Current Protocols in Immunology', Wiley Interscience, 1997. Alternatively, antibody production may be examined, using

standard immunoassays or plaque-analysis assays, or assessed by intrauterine protection of a foetus, see ~Current Protocols in Immunology'.

Additionally, the instant claims recite 'an immunogenic determinant comprising any induced stress protein and any antigenic peptide *obtained* from, a cell which has been infected with....". Srivastava et al teach an immunogenic determinant comprising any induced stress protein and any antigenic peptide. The claims are product-by-process claims. "The patentability of a product does not depend upon its method of production. If the product in [a] product-by-process claim is the same as or obvious from a product of the prior art, [then] the claim is unpatentable even though the prior [art] product was made by a different process." In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. In re Marosi, 218 USPQ 289, 292 (Fed. Cir. 1983). There does not appear to be a structural difference between the product claimed and the product taught by the prior art, e.g., the claimed compositions solely comprise an immunogenic determinant any complex comprising a stress protein and an antigenic peptide fragment. While a specific stressor may cause more stress protein and stress protein complexes to be induced, it does not appear to change the structure of the complex, nor does the claim require a specific level of complex. Srivastava et al do not solely teach constitutively expressed complexes. Srivastava discloses the claimed compositions

produced by a stress process and isolated from natural sources, produced in situ. The bacterial heat shock protein (see Table 1 and definitions) is complexed together with an antigenic peptide fragment from a bacteria (see col. 7, line 7 "Chlamydia"), fungus, or protozoa, wherein the heat shock protein complex is isolated from natural sources (see col. 21, line 28). Accordingly, Srivastava et al anticipates the claimed compositions.

6. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 8:00 AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645

5/18/11